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The Foreign Patents Branch of the United States Patent and Trademark Office is in need of some assistance from your office in obtaining a copy of **Denmark Patent Application 9800727**, this in accordance with the exchange agreement between our respective patent offices. The document may be sent too my attention at the following address:

United States Patent and Trademark Office
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Attn.: Eugene T. Stevenson, Jr.
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If possible, you may fax the patent to **(703) 308-1000**. If there is anything you require of our department in the future, please contact us. Again, thank you for your assistance in this matter.

Sincerely,

Eugene T. Stevenson, Jr.

Eugene T. Stevenson, Jr., Branch Chief
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Country	Patent No.	Pages	Tech Center
DK	9800727		

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☐ 1. Document ID: DK 9800727 A

L1: Entry 1 of 1 File: DWPI May 28, 1998

DERWENT-ACC-NO: 1998-533654
DERWENT-WEEK: 199846

TITLE: Treatment of GABA-uptake related disorders - used for e.g. luster headaches, dementia, alcohol withdrawal symptoms, spasticity, growth disturbances, tardive dyskinesia or alcohol abuse

PATENT-ASSIGNEE:

ASSIGNEE	CODE
NOVO-NORDISK AS	NOVO

PRIORITY-DATA: 1998DK-0000727 (May 28, 1998)

PATENT-FAMILY:

PUB-NO	PUB-DATE	LANGUAGE	PAGES	MAIN-IPC
DK 9800727 A	May 28, 1998	N/A	001	A61K031/445

APPLICATION-DATA:

PUB-NO	APPL-DATE	APPL-NO	DESCRIPTOR
DK 9800727A	May 28, 1998	1998DK-0000727	N/A

INT-CL (IPC): A61K 31/445

ABSTRACTED-PUB-NO: DK 9800727A
BASIC-ABSTRACT:

Method for the treatment of GABA-uptake related disorders such as cluster headaches, dementia, alcohol withdrawal symptoms, spasticity, growth disturbances, tardive dyskinesia, alcohol abuse, stuttering, hot flushes, Huntingtons Choerea, Gilles di le Tourettes syndrome, incontinence, diabetic neuropathy and postherpetic neuralgia.

CHOSEN-DRAWING: Dwg.0/0

TITLE-TERMS: TREAT UPTAKE RELATED DISORDER HEADACHE DEMENTIA ALCOHOL WITHDRAW SYMPTOM SPASTICITY GROWTH DISTURB TARDIVE DYSKINESIA ALCOHOL ABUSE

DERWENT-CLASS: B04

CPI-CODES: B14-C01; B14-D01; B14-J01A4; B14-J01B3; B14-J02; B14-J05A; B14-J07; B14-M01A; B14-N07D; B14-N11;

SECONDARY-ACC-NO:
CPI Secondary Accession Numbers: C1998-160081

Patent- og Varemærkestyrelsen
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Patentansøgning

Se vejledning til de enkelte punkter

1. Gebyrer:

- [x] Ansøgningsgebyr
- [ ] Kravgebyr
- [ ] Tillægsgebyr for hastebehandling
- [ ] Tillægsgebyr for behandling af engelsksproget beskrivelse

2. Ansøgers/fuldmægtigs referencenr.:
5257.009-DK,PeHo

3. International indleveringsdag:
Internationalt ansøgningsnr.:
- [ ] Kapitel I
- [ ] Kapitel II

4. Ansøger (fulde navn og adresse):
- [ ] Flere ansøgere på bagsiden.

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6a. Opfinder (fornavn, efternavn, adresse):
- [ ] Flere opfindere på bagsiden.

7. Opfindelsens benævnelse:

8. Prioritetspåstand(e):
- [ ] Flere prioritetspåstande på bagsiden.

Dato	Land	Nr.
Dato	Land	Nr.
Dato	Land	Nr.

9. [ ] Ansøgningen omfatter deponering af mikroorganisme-kultur(er), som angivet i patentlovens § 8a, stk. 1.

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14. Dato og underskrift: 28.05.1998

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12. Bilagsfortegnelse:

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Fig. nr. _____ ønskes publiceret sammen med sammendraget.

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A. Title of the invention

Treatment of GABA-uptake related disorders

B. Field of the invention

The present invention relates to a method for the treatment of GABA-uptake related disorders such as cluster headaches, dementia, alcohol withdrawal symptoms, spasticity, growth disturbances, tardive dyskinesia, alcohol abuse, stuttering, hot flushes, Huntingtons Choerea, Gilles de la Tourettes syndrome, incontinence, diabetic neuropathy and postherpetic neuralgia.

The present invention also relates to a compound for use in such methods.

The present invention further provides the use of such compound or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for use in the treatment of GABA-uptake related disorders, .

C. Background of the Invention

US Patent No. 5,010,090 discloses a class of compounds that exhibit γ-amino butyric acid uptake (GABA-uptake) inhibitory properties and said compounds are valuable in the treatment of anxiety, epilepsy and muscular and movement disorders.

Anxiety includes obsessive-compulsive disorder, panic disorder, social phobias, post-traumatic stress disorders, agoraphobia and the like. (Peter Charlish, Pharmaprojects Magazine, June 1997, page 6-8).

Epilepsy includes infantile spasms, myoclonic seizures, absences and the Lennox-Gastaut syndrome.

In PCT publication WO 96/34865 the use of GABA-uptake inhibitors in the treatment of pain are described.

In PCT publication WO 95/18615 the use of GABA-uptake inhibitors in the treatment of neurogenic pain or inflammation are described.

In PCT publication WO 97/02813 the use of GABA-uptake inhibitors in the treatment of sleep disorders are described.

In PCT publication WO 96/15782 the use of GABA-uptake inhibitors in the treatment of migraine are described.

The R-isomer of N-(4,4-di(3-methylthien-2-yl)but-3-enyl)-nipecotic acid, as disclosed as a GABA-uptake inhibitor in US Patent No. 5,010,090, is in the following referred to by its generic name, tiagabine (INN).

Tiagabine and its pharmaceutically active salts has been found useful in the treatment of epilepsy and all the other above mentioned disorders related to the GABA-uptake.

D. Description of the invention

It has now been found that tiagabine also has potential therapeutic utility for treating disorders such as cluster headaches, dementia, alcohol withdrawal symptoms, spasticity, growth disturbances, tardive dyskinesia, alcohol abuse, stuttering, hot flushes, Huntingtons Choerea, Gilles de la Tourettes syndrome, incontinence, diabetic neuropathy and postherpetic neuralgia.

Accordingly, the present invention provides a method for treating disorders such as cluster headaches, dementia, alcohol withdrawal symptoms, spasticity, growth disturbances, tardive dyskinesia, alcohol abuse, stuttering, hot flushes, Huntingtons Choerea, Gilles de la Tourettes syndrome, incontinence, diabetic neuropathy and postherpetic neuralgia which method comprises administering an effective, non-toxic amount of tiagabine or a pharmaceutically acceptable salt thereof, to human or non-human animals suffering from cluster headaches, dementia, alcohol withdrawal symptoms, spasticity, growth disturbances, tardive dyskinesia, alcohol abuse, stuttering, hot flushes, Huntingtons Choerea, Gilles de

la Tourettes syndrome, incontinence, diabetic neuropathy and postherpetic neuralgia.

The present invention also provides the use of tiagabine or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for use in the treatment of disorders such as cluster headaches, dementia, alcohol withdrawal symptoms, spasticity, growth disturbances, tardive dyskinesia, alcohol abuse, stuttering, hot flushes, Huntingtons Choerea, Gilles de la Tourettes syndrome, incontinence, diabetic neuropathy and postherpetic neuralgia.

Examples of pharmaceutically acceptable salts of tiagabine are tiagabine hydrochloride, but tiagabine may also be prepared in the form of other pharmaceutically acceptable salts, especially acid-addition salts, including salts of organic acids and mineral acids.

Examples of such salts include salts of organic acids such as formic acid, fumaric acid, acetic acid, propionic acid, glycolic acid, lactic acid, pyruvic acid, oxalic acid, succinic acid, malic acid, tartaric acid, citric acid, benzoic acid, salicylic acid and the like.

Suitable inorganic acid-addition salts include salts of hydrobromic, sulphuric and phosphoric acids and the like.

The acid addition salts may be obtained as the direct products of compound synthesis.

In the alternative, the free base may be dissolved in a suitable solvent containing the appropriate acid, and the salt isolated by evaporating the solvent or otherwise separating the salt and solvent.

A preferred salt is crystalline tiagabine hydrochloride monohydrate or anhydrate.

A tiagabine medicament, for use in the treatment of disorders such as cluster headaches, dementia, alcohol withdrawal symptoms, spasticity, growth disturbances, tardive dyskinesia, alcohol abuse, stuttering, hot flushes, Huntingtons Choerea, Gilles de la Tourettes syndrome, incontinence, diabetic neuropathy and postherpetic neuralgia may be prepared by admixture of tiagabine or a salt thereof with an appropriate carrier, which may contain a diluent, binder, filler, disintegrant, flavouring agent, colouring agent, lubricant or preservative in conventional manner.

Pharmaceutical compositions

The compound of the invention, together with a conventional adjuvant, carrier or diluent, and if desired in the form of a pharmaceutically acceptable acid addition salt thereof, may be placed into the form of pharmaceutical com-positions and unit dosages thereof, and in such form may be employed as solids, such as tablets or filled capsules, or liquids, such as solutions, sus-pensions, emulsions, elixirs, or capsules filled with the same, all for oral use, in the form of suppositories for rectal administration; or in the form of sterile injectable solutions for parenteral use (including subcutaneous administration and infusion). Such pharmaceutical compositions and unit dosage forms thereof may comprise conventional ingredients in conventional proportions, with or without additional active compounds or principles, and such unit dosage forms may contain any suitable effective amount of tiagabine commensurate with the intended daily dosage range to be employed. Tablets containing five (5) milligrams of active ingredient or, more broadly, one (1) to hundred (100) milligrams, per tablet, are accordingly suitable representative unit dosage forms.

The compounds of this invention can thus be used for the formulation of pharmaceutical preparation, e.g. for oral and parenteral administration to mammals including humans, in accordance with conventional methods of galenic pharmacy.

Conventional excipients are such pharmaceutically acceptable organic or inorganic carrier substances suitable for parenteral or enteral application which do not deleteriously react with the active compounds.

Examples of such carriers are water, salt solutions, alcohols, polyethylene glycols, polyhyroxyethoxylated castor oil, gelatine, lactose amylose, magnesium stearate, talc, silicic acid, fatty acid monoglycerides and diglycerides, pentaerythritol fatty acid esters, hydroxymethylcellulose and polyvinylpyrrolidone.

The pharmaceutical preparations can be sterilised and mixed, if desired, with auxiliary agents, emulsifiers, salt for influencing osmotic pressure, buffers and/or colouring substances and the like, which do not deleteriously react with the active compounds.

For parenteral application, particularly suitable are injectable solutions or suspensions, preferably aqueous solutions with the active compound dissolved in polyhydroxylated castor oil.

Ampoules are convenient unit dosage forms.

Tablets, dragees, or capsules having talc and/or carbohydrate carrier or binder or the like, the carrier preferably being lactose and/or corn starch and/or potato starch, are particularly suitable for oral application. A syrup, elixir or the like can be used in cases where a sweetened vehicle can be employed.

Generally, the compounds of this invention are dispensed in unit form comprising 0.05-100 mg in a pharmaceutically acceptable carrier per unit dosage.

The dosage of the compounds according to this invention is 0.1-300 mg/day, preferably 1-100 mg/day, when administered to patients, e.g. humans, as a drug.

Examples of tablets which may be prepared by conventional tabletting techniques are:

COMPOSITION I

Tiagabine hydrochloride	5.0 mg
Lactosum	7.0 mg Ph.Eur.
AvicelTM	31.4 mg
AmberliteTMIRP 88	1.0 mg
Magnesii stearas	0.25 mg Ph.Eur.

or

COMPOSITION II

Tiagabine hydrochloride	8 mg
Polyethylene Glycol 6000, NF	16 mg
Lactose, anhydrous, NF	279 mg
δ-Tocopherol, Ph.Eur	0.8 mg
Talc, Ph. Eur.	16 mg

CLAIMS

1. The use of tiagabine or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for use in the treatment of disorders such as cluster headaches, dementia, alcohol withdrawal symptoms, spasticity, growth disturbances, tardive dyskinesia, alcohol abuse, stuttering, hot flushes, Huntingtons Choerea, Gilles de la Tourettes syndrome, incontinence, diabetic neuropathy and postherpetic neuralgia.

2. The use according to claim 1 wherein tiagabine is in its form of hydrochloride monohydrate or anhydrate.

3. A method of treating disorders such as cluster headaches, dementia, alcohol withdrawal symptoms, spasticity, growth disturbances, tardive dyskinesia, alcohol abuse, stuttering, hot flushes, Huntingtons Choerea, Gilles de la Tourettes syndrome, incontinence, diabetic neuropathy and postherpetic neuralgia in human or non-human animals, which method comprises administering an effective, non-toxic amount of tiagabine or a pharmaceutically acceptable salt thereof, to human or non-human animals suffering from said disorders.

4. A use according claim 1 wherein the medicament is adapted for oral administration.

5. A use according to claim 1 wherein the medicament is adapted for parenteral administration.

6. A use according to claim 1 wherein the medicament is in a unit dose form containing from 0.05 to 100 mg of tiagabine or a pharmaceutically acceptable salt thereof.

7. A method according to claim 3 in which the tiagabine or a pharmaceutically acceptable salt thereof is adapted for oral administration.

8. A method according to claim 3 in which the tiagabine or a pharmaceutically acceptable salt thereof is adapted for parenteral administration.

9. A method according to claim 3 wherein the tiagabine or a pharmaceutically acceptable salt thereof is in a unit dose form containing from 0.05 to 100 mg of tiagabine or a pharmaceutically acceptable salt thereof.

ABSTRACT

The present invention relates to a method for the treatment of GABA-uptake related disorders such as cluster headaches, dementia, alcohol withdrawal symptoms, spasticity, growth disturbances, tardive dyskinesia, alcohol abuse, stuttering, hot flushes, Huntingtons Choerea, Gilles de la Tourettes syndrome, incontinence, diabetic neuropathy and postherpetic neuralgia.